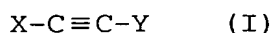


Preparation of organic alkyne compounds

The present invention relates to a process for preparing organic
5 alkyne compounds of the formula I



by reacting organic halogen compounds of the formula Ia

10



with organic terminal alkyne compounds of the formula Ib

15



where X and Y are identical or different organic radicals and Hal
is chlorine or bromine, in inert solvents under the action of
microwave energy, in the presence of at least one metal compound
20 and at least one base.

Under the customary conditions of the Sonogashira reaction, aryl
or alkenyl halides are reacted with terminal alkyne compounds
under palladium and copper salt catalysis at elevated temperature
25 to give correspondingly substituted alkyne compounds.

A distinct reduction in the reaction time can be achieved by
carrying out the reaction under the action of microwave
radiation.

30

For instance, J.-X. Wang et al. (J. Chem. Research (S), 2000, p.
536-537) describe reactions of different terminal alkynes with
organic iodine compounds in the presence of copper(I)
iodide/triphenylphosphine and potassium carbonate in
35 dimethylformamide (DMF). The comparison of the reactions show in
table 2 of this publication, on the one hand under reflux of DMF,
and on the other hand under the action of a microwave radiation
source having an output of 375 W shows impressively that when
comparable yields are obtained, the reactions in the latter case
40 proceed more quickly than in the former case by factors of from
48 to 144.

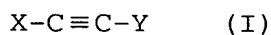
Investigations of solvent-free reactions of aryl, heteroaryl and
vinyl iodides with terminal alkynes in the presence of
45 palladium/copper(I) iodide/triphenylphosphine and potassium
fluoride supported on aluminum oxide under the action of
microwave radiation have been carried out by G.W. Kabalka et al.

(Tetrahedron Lett. 41, 2000, p. 5151-5154). The authors mention (p. 5152) that aryl chlorides and bromides did not react and that the starting materials were recovered unchanged.

- 5 We have now been found that, surprisingly, organic chlorine and bromine compounds can be reacted with terminal organic alkyne compounds to give alkyne derivatives in good to very good yields.

Accordingly, a process has been found for preparing organic

- 10 alkyne compounds of the formula I



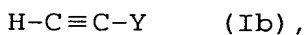
by reacting organic halogen compounds of the formula Ia

15



with organic terminal alkyne compounds of the formula Ib

20



where X and Y are identical or different organic radicals

in inert solvents under the action of microwave energy,

25

in the presence of at least one metal compound and at least one base, wherein Hal is chlorine or bromine.

In this context, inert solvents are liquids or liquid mixtures

- 30 which under the reaction conditions react neither with the reactants nor with the products.

In particular, such inert solvents are polar, aprotic liquids, since the use of protic liquids may lead to undesired secondary

- 35 reactions which are triggered off by protonation.

To simplify the discussion, the terms "solvent" and "dissolve" will hereinbelow be used, even when in individual cases, for

example, the base or bases or metal compound or metal compounds

- 40 used are not completely dissolved, but are instead in suspension (or emulsion).

Preference is given to using those metal compounds which comprise a metal selected from the group consisting of magnesium, calcium,

- 45 strontium, barium, titanium, zirconium, hafnium, iron, ruthenium, osmium, cobalt, rhodium, iridium, nickel, palladium, platinum,

3

copper, silver, gold, zinc, cadmium and mercury. Particular preference is given to using copper compounds.

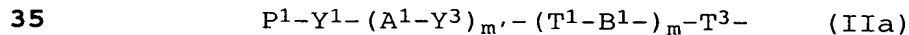
Emphasis is given to the metal halide compounds, in particular the chlorides and bromides, but also the iodides, of the metals mentioned. When these halides form adducts with triarylphosphines, for example triphenylphosphine, they are advantageously used in the form of these adducts.

10 Metal compounds further include the metals themselves, in particular the abovementioned metals in elemental form. Furthermore, combinations of more than one metal compound, more than one metal, and also combinations of metals and metal compounds may be used. The metal species which is catalytically
15 active in the reaction does not necessarily have to be identical to the metal compounds added, but can instead only be formed in situ by reaction with the reactants and/or the base or bases.

The organic radicals X and Y are saturated or unsaturated
20 hydrocarbon radicals, and also hydrocarbon radicals which contain both saturated and unsaturated moieties. The hydrocarbon radicals may further contain customary heteroatoms, such as nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, bromine or iodine. The organic radicals X and Y customarily have molar
25 masses of up to about 600 g/mol. However, in individual cases, the molar masses of the X and Y radicals may also be higher.

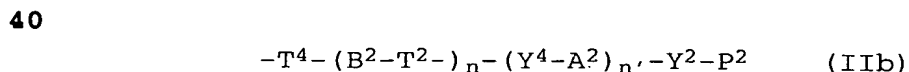
Preferred organic radicals X and Y contain saturated or unsaturated carbo- or heterocyclic radicals where both -Hal, i.e.
30 chlorine or bromine, and $H-C\equiv C-$ are bonded directly to the saturated or unsaturated carbo- or heterocyclic radicals.

In particular, X is a radical of the formula IIa



and

Y is a radical of the formula IIb



where

45

4

P¹ and P² are each independently hydrogen, C₁-C₂-alkyl, a polymerizable group, a group suitable for polymerization or a radical which carries a polymerizable group or a group suitable for polymerization,

5

or

P¹ and/or P² each corresponds to a radical P^{1'} and/or P^{2'} which denotes a precursor group which is stable under the reaction conditions which can be reacted to give the corresponding polymerizable group or group suitable for polymerization P¹ and/or P² or the radicals P¹ and/or P² which carry a polymerizable group or a group suitable for polymerization,

15 Y¹, Y², Y³ and Y⁴ are each independently a single chemical bond, -O-, -S-, -CO-, -CO-O-, -O-CO-, -CO-N(R)-, -(R)N-CO-, -O-CO-O-, -O-CO-N(R)-, -(R)N-CO-O- or -(R)N-CO-N(R)-,

20 B¹ and B² are each independently a single chemical bond, -C≡C-, -O-, -S-, -CO-, -CO-O-, -O-CO-, -CO-N(R)-, -(R)N-CO-, -O-CO-O-, -O-CO-N(R)-, -(R)N-CO-O- or -(R)N-CO-N(R)-,

25 each R is, independently and irrespective of the meaning in each of Y¹ to Y⁴, B¹ and B², hydrogen or C₁-C₄-alkyl,

A¹ and A² are each independently spacers having from 1 to 30 carbon atoms,

30

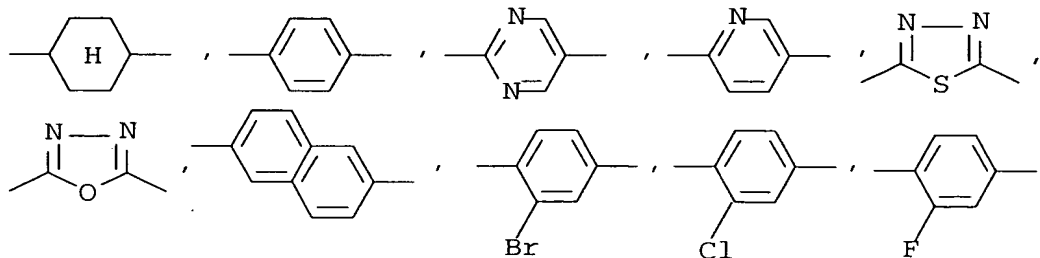
T¹, T², T³ and T⁴ are each independently bivalent, saturated or unsaturated, carbo- or heterocyclic radicals and

m', m, n' and n are each independently 0 or 1.

35

The T¹ to T⁴ radicals in the formulae IIa and IIb are in particular those selected from the group consisting of

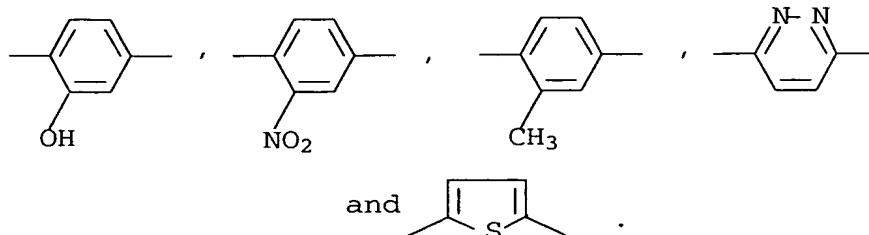
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5

5



Useful C_1 - C_{12} -alkyl radicals for P^1 and P^2 in formula I include

10 branched and unbranched C_1 - C_{12} -alkyl chains, for example methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl, n-hexyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl,

15 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl,

20 1-ethyl-2-methylpropyl, n-heptyl, n-octyl, 2-ethylhexyl, n-nonyl, n-decyl, n-undecyl and n-dodecyl.

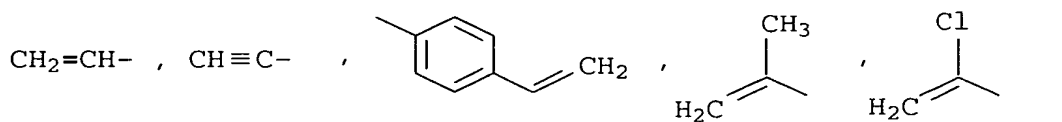
Preferred P^1 and P^2 alkyl radicals are the branched and unbranched C_1 - C_6 -alkyl chains, such as methyl, ethyl, n-propyl,

25 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, n-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl and n-hexyl.

Useful polymerizable groups or groups which are suitable for

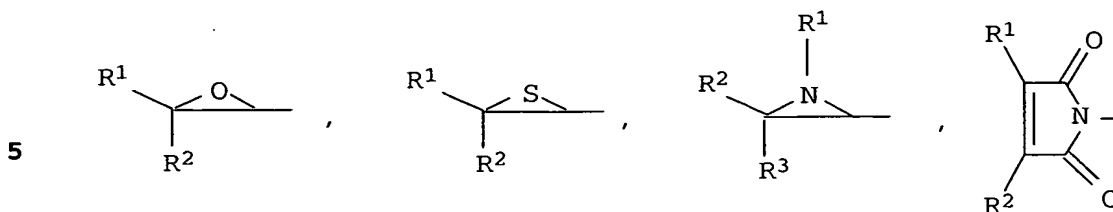
30 polymerization or radicals which carry a polymerizable group or a group suitable for polymerization (such groups or radicals are referred to hereinbelow simply as "reactive radicals") for P^1 and P^2 are in particular:

35



40

45



-N=C=O, -N=C=S, -O-C≡N, -COOH, -OH or -NH₂,

- 10 where the R¹ to R³ radicals can be identical or different and are each hydrogen or C₁-C₄-alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl.

Useful polymerizable groups for P¹ and P² are in particular the
15 acrylate, methacrylate and vinyl radicals.

Useful C₁-C₄-alkyl radicals in the -CO-N(R)-, -(R)N-CO-,
-O-CO-N(R)-, -(R)N-CO-O- and -(R)N-CO-N(R)- groups listed under
the bridging units Y¹ to Y⁴, B¹ and B² include methyl, ethyl,
20 n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.
When one or two R radicals are present in the Y¹ to Y⁴, B¹ and B²
units, any R radicals present in the remaining units may be
identical or different. The same applies to the case where there
are two R radicals in one unit.

25

Useful spacers A¹ and A² include all groups known to those skilled
in the art for this purpose. The spacers generally have from one
to 30, preferably from one to 12, more preferably from one to
six, carbon atoms and consist of predominantly linear aliphatic
30 groups. They may be interrupted in the chain by, for example,
nonneighboring oxygen or sulfur atoms or imino or alkylimino
groups, for example methylimino groups. Useful substituents for
the spacer chain include fluorine, chlorine, bromine, cyano,
methyl and ethyl.

35

Examples of representative spacers include:

-(CH₂)_u-, -(CH₂CH₂O)_vCH₂CH₂-, -CH₂CH₂SCH₂CH₂-, -CH₂CH₂NHCH₂CH₂-,

40

-CH₂CH₂N(CH₃)-CH₂CH₂-, -(CH₂CH(CH₃)CHO)_wCH₂CH(CH₃)-, -(CH₂)₆CH(CH₃)- or -CH₂CH₂CH(CH₃)Cl-,

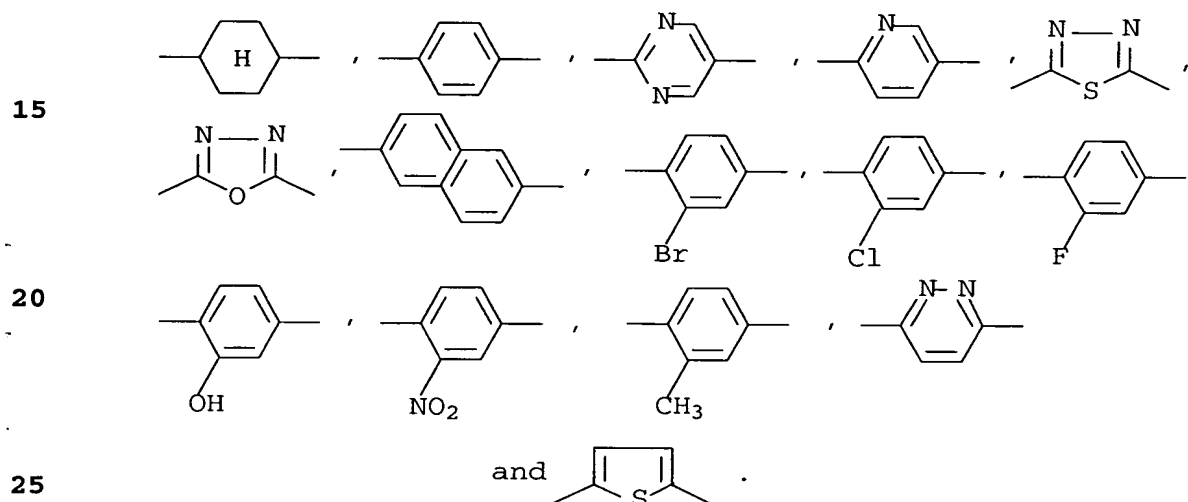
where u, v and w are integers and u is from 1 to 30, preferably
45 from 1 to 12, v is from 1 to 14, preferably from 1 to 5, and w is
from 1 to 9, preferably from 1 to 3.

7

Preferred spacers are ethylene, propylene, n-butylene, n-pentylene and n-hexylene.

The T¹ to T⁴ radicals are ring systems which may be substituted by
 5 fluorine, chlorine, bromine, cyano, hydroxyl, formyl, nitro, C₁-C₂₀-alkyl, C₁-C₂₀-alkoxy, C₁-C₂₀-alkoxycarbonyl, C₁-C₂₀-monoalkylaminocarbonyl, C₁-C₂₀-alkylcarbonyl, C₁-C₂₀-alkylcarbonyloxy or C₁-C₂₀-alkylcarbonylamino.

10 Preferred T¹ to T⁴ radicals are:



When the reactive P¹ and/or P² radicals are unstable under the reaction conditions, the reactants

30 P¹'-Y¹-(A¹-Y³)_m-(T¹-B¹-)_m-T³-Hal and/or

H-C≡C-T⁴-(B²-T²-)_n-(Y⁴-A²)_n-Y²-P²'

may be used as starting materials where the P¹' and/or P²'
 35 radicals are precursor groups which are stable under the reaction conditions and are converted to or substituted by the corresponding reactive P¹ and/or P² radicals in a subsequent step.

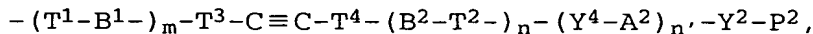
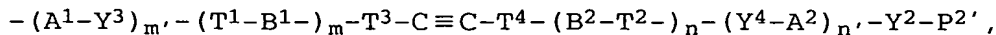
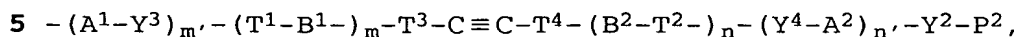
Compounds which, for example, have the construction

40 P¹'-Y¹-(A¹-Y³)_m-(T¹-B¹-)_m-T³-C≡C-T⁴-(B²-T²-)_n-(Y⁴-A²)_n-Y²-P²'

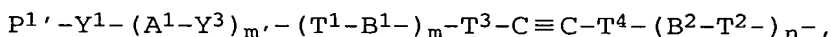
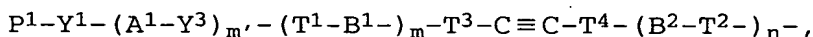
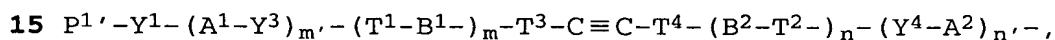
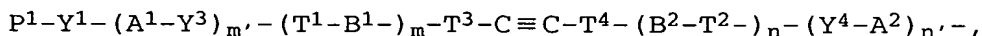
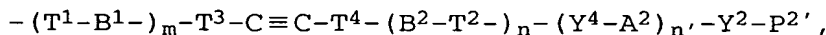
may be regarded as direct products of the preparative process according to the invention.

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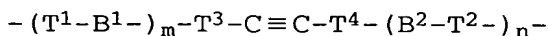
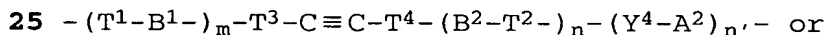
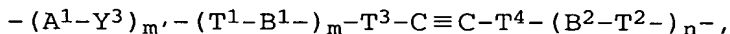
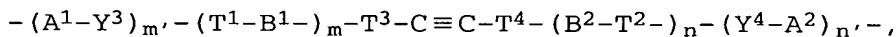
Owing to retrosynthetic considerations, it may also be sensible to prepare the alkyne compounds by the process according to the invention which correspond to the fragments



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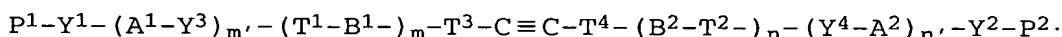


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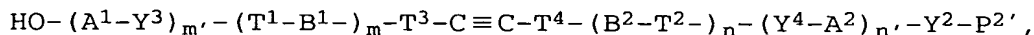
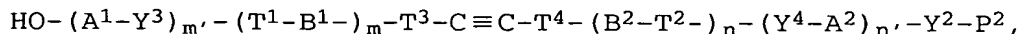
and then convert these in one or more subsequent steps using the appropriate complementary compounds to the target compounds

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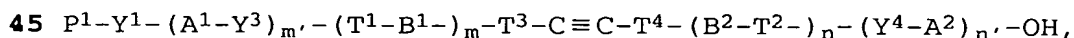
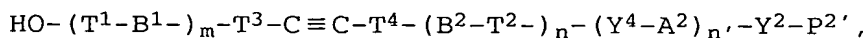
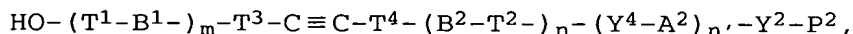


Examples of compounds to which the above-listed fragments correspond include

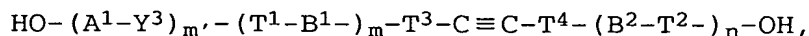
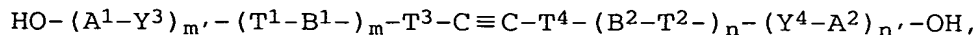
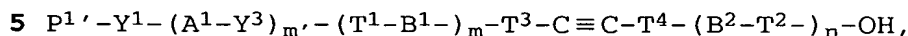
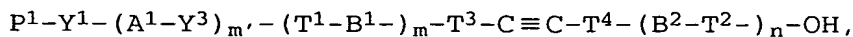
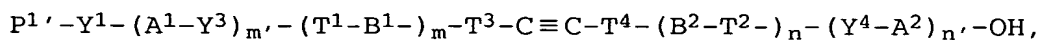
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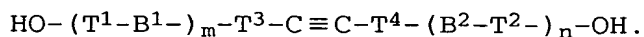
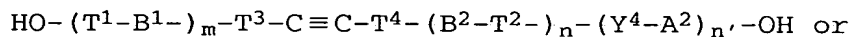
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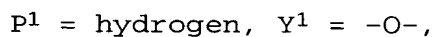
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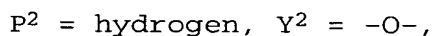
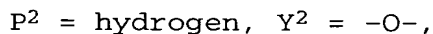
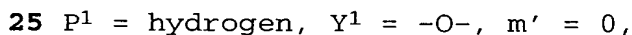
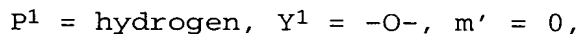
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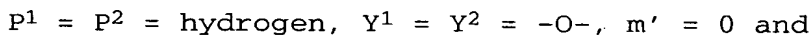
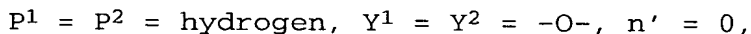
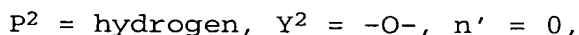
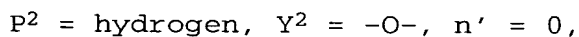
15 According to the definition of the X and Y radicals in the formulae IIa and IIb, the variables in the compounds listed are, in the same order in which they were listed, as follows:



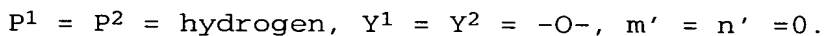
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Further, the hydroxyl group may be replaced by, for example, a carboxyl group ($P^1 = \text{hydrogen}$ and $Y^1 = -OCO-$ and/or $P^2 = \text{hydrogen}$ and $Y^2 = -COO-$). In the difunctional compounds, both hydroxyl and carboxyl groups may also be present.

45

10

These hydroxyl or carboxylic acid or hydroxyl/carboxylic acid compounds which are given by way of example are again to be regarded as direct products of the preparative process according to the invention.

5

The reactants of the formulae Ia and Ib are customarily dissolved in a molar ratio of from 2:1 to 1:2 together with the at least one metal compound and the at least one base in the inert solvent. The solution is normally prepared at room temperature, but in individual cases, may also be prepared at higher or lower temperatures.

The temperature during the actual reaction under the action of microwave radiation is not critical. Customarily, the reaction is carried out at temperatures from room temperature to the boiling temperature of the solvent used.

Preference is given to using dimethylformamide ("DMF"), N-methylpyrrolidone ("NMP") or a mixture of the two as solvent. Particular preference is given to using DMF as solvent (or as suspending medium) in the process according to the invention.

Preference is given to selecting the at least one base from the group consisting of alkali metal carbonates, alkali metal phosphates and tri(C₁-C₄-alkyl)amines, and emphasis is given to the alkali metal carbonates.

The group of suitable bases includes in particular sodium carbonate, potassium carbonate, sodium phosphate and potassium phosphate, trimethyl-, triethyl- and triisopropylamine.

Particular preference is given to using potassium carbonate.

In individual cases, the addition of potassium iodide may also be advantageous for the reaction. Whether there is such a positive effect and how much potassium iodide should optionally be added can be easily determined by preliminary experiments.

The output of the microwave radiation source is customarily from ten to hundreds of watts and should be selected according to the volume of the reaction batch. The correct power of the radiation source is customarily known to those skilled in the art and/or can be easily determined by preliminary experiments.

The alkyne compounds obtained are worked up and purified by customary organic synthesis methods.

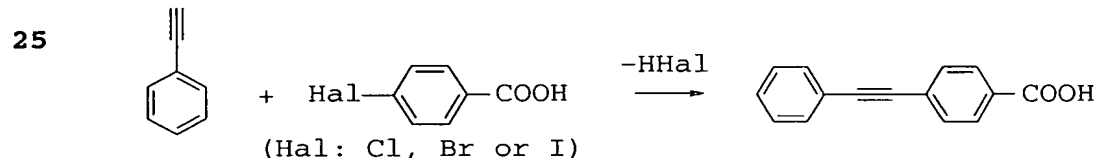
Examples:

The experiments described hereinbelow use the following:

5	Substance	Source	Purity
	4-Chlorobenzoic acid	Acros	>99%
	4-Bromobenzoic acid	Merck	>99%
	4-Iodobenzoic acid	EMKA-Chemie	>99%
10	Phenylacetylene	Aldrich	>98%
	Copper(I) iodide	Merck	>99%
	Triphenylphosphine	Merck	>99%
	Potassium carbonate (ground)	Merck	>99.9%
15	Dimethylformamide ("DMF")	BASF	>99%
	Potassium iodide	J.T.Baker	>99%

20 Experimental procedure:

General reaction equation:



- 30 5 mmol of 4-halobenzoic acid (halo: chloro, bromo or iodo), 7.5 mmol of phenylacetylene, 0.5 mmol of copper(I) iodide, 1.0 mmol of triphenylphosphine, 7.5 mmol of potassium carbonate and 10 ml of DMF were initially charged under an argon atmosphere into a 100 ml four-neck flask provided with a magnetic stirrer,
- 35 heated within 5 min to a temperature of 155°C and subjected at reflux for 20 min to the maximum radiation output of a microwave device (MLS-Ethos 1600; unpulsed; magnetron frequency 2450 MHz; maximum output 375 W).
- 40 The workup was carried out by filtering off the solid (substantially in potassium carbonate), washing with 100 ml of dichloromethane and extracting the solution obtained three times with 50 ml each time of a saturated, aqueous sodium chloride solution. The dichloromethane solution was dried over sodium
- 45 sulfate and then the solvent was removed on a rotary evaporator.

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For comparative purposes, experiments were also carried out with the addition of 0.5 mmol of potassium iodide. The amounts of the remaining substances used were unchanged; the experimental procedure and workup were likewise identical to those described 5 above.

Results:

The experimental results are reported in the following table.

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Example	Yield (% of theory)	Potassium iodide addition	4-Halobenzoic acid Halo =
1 (Comparative)	33.0	-	I
15 2	74.4	-	Cl
3	56.5	+	Cl
4	54.5	-	Br
5	38.6	+	Br

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When 4-iodobenzoic acid was used (example 1 (comparative), the lowest yields by far were obtained, but when 4-bromo- and in particular 4-chlorobenzoic acid were used (examples 4 and 5, and 2 and 3 respectively), distinctly higher yields of the desired target compound were obtained. In the experiments carried out 25 here, the addition of potassium iodide (examples 3 and 5) caused a deterioration compared to the potassium iodide-free experimental procedure (examples 2 and 4). However, it is conceivable that, in individual cases, the addition of potassium iodide may have an advantageous effect.

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